Comparison between Intraperitoneal and Oral Methylphenidate Administration: A Microdialysis and Locomotor Activity Study[1]

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ABSTRACT

The therapeutic and stimulant properties of methylphenidate (MP), a drug commonly prescribed for the treatment of attention deficit hyperactivity disorder, have been attributed to increases in synaptic dopamine (DA) concentrations resulting from the blockade of DA transporters. In addition to obvious difficulties inherent in any interspecies comparison, interpretation of preclinical studies done with MP is further complicated by different routes of administration in animals (i.v. and i.p.) compared with humans (oral). In the present study we compared the effects of i.p. and intragastric (oral) MP both on rat nucleus accumbens DA assessed by in vivo microdialysis and on locomotor activity measured in a photocell apparatus. We also compared regional brain uptake and plasma levels of [3H]MP after administration of 5 mg/kg via both routes. Intraperitoneal MP (5 and 10 mg/kg) was approximately twice as potent as intragastric MP in terms of increasing extracellular DA levels and in stimulating locomotion. This was consistent with the higher brain uptake of [3H]MP when given i.p. rather than intragastrically. The dose of 2 mg/kg produced significant increases in both measurements when administered i.p., but not intragastrically. This study shows that relatively low doses of MP (2 mg i.p. and 5 mg intragastric) significantly increase extracellular DA and locomotor activity and indicates that the differences in the neurochemical and behavioral effects of MP between the intragastric and the i.p. routes are due to central drug bioavailability.

Over the past decade increased recognition of attention deficit hyperactivity disorder (Swanson et al., 1998) has led to a dramatic increase in the use of methylphenidate (Ritalin, MP), a psychostimulant commonly prescribed to treat this disorder. Despite this widespread use, the mechanisms by which MP exerts its therapeutic effects remain poorly understood. Although a considerable number of preclinical studies have been completed, their interpretation is limited by the fact that i.p. and i.v. routes have been used, whereas the oral route is used clinically. Moreover, most studies have used doses significantly higher (2–15 mg/kg i.v. or 10–50 mg/kg i.p.) than those used clinically in humans (0.3–1 mg/kg; Sprague and Sleator, 1977). Studies with doses that are therapeutically relevant (0.6–10 mg/kg i.p. or s.c.) have predominantly investigated sensitization and tolerance to motor-activating and stereotypic effects of MP (McNamara et al., 1993; Gaytan et al., 1997; McDougall et al., 1999). Higher

doses of MP lead to a greater incidence of side effects, including sleep disturbances and irritability in children (Cole, 1975). To our knowledge, the only two studies that have investigated the effects of oral MP in rodents focused on its pharmacokinetic profile in brain and plasma, and not on the concomitant behavioral or neurochemical effects of the drug (Wargin et al., 1983; Patrick et al., 1987).

The therapeutic effects of MP as well as its psychostimulant properties are thought to be related to its ability to increase extracellular dopamine (DA) in the mesocorticolimbic system (Castellanos et al., 1996), secondary to blockade of DA transporters (Ritz et al., 1987). Similarly, the reinforcing effects of cocaine and cocaine-like drugs also are associated with their ability to block the DA transporter. This has led to serious concerns regarding the potential reinforcing or addictive properties of MP. However, despite the pharmacological similarities between MP and cocaine, including similar potency at the DA transporter (Volkow et al., 1995; Gatley et al., 1999), its abuse is much less frequent (NIDA-CEWG, 1995) and is mainly restricted to the i.v. or intranasal route of administration with very infrequent oral abuse (Parran and Jasinski, 1991). The rare occurrence of oral abuse is probably related to the slow rate of DA transporter blockade achieved by oral MP because the reinforcing effects of psy-

ABBREVIATIONS: MP, methylphenidate; DA, dopamine; LCGU, local cerebral glucose utilization; NACC, nucleus accumbens.

chostimulant drugs are thought to be related, at least in part, to a rapid rate of binding to DA transporters (Stathis et al., 1995) and subsequently, a rapid increase in synaptic DA (Balster and Schuster, 1973). Thus, although i.v. MP produces a "high", which cocaine abusers report to be similar to that induced by i.v. cocaine (Wang et al., 1997), oral MP with a slower onset of transporter blockade does not produce a high in normal subjects (Volkow et al., 1998).

Dose-related effects of MP were clearly demonstrated by Porrino and coworkers. They showed that local cerebral glucose utilization (LCGU) in the rat nucleus accumbens (NACC), a brain region associated with the reinforcing effects of drugs of abuse (Di Chiara, 1999), was stimulated by a low dose of MP (1.25 mg/kg i.v.), but not by a high dose (15 mg/kg). However, higher doses dramatically increased LCGU in the extrapyramidal system (Porrino and Lucignani, 1987). A similar dose-related pattern was observed with amphetamine (Porrino et al., 1984). These authors later demonstrated that behaviorally equivalent doses of i.v., but not i.p. cocaine, produced increases in LCGU in NACC (Porrino, 1993). This similarity in the distribution of changes in LCGU led the authors to propose a significant role of the NACC in the therapeutic response of hyperactive children to psychostimulant medications. Taken together, these data suggest the importance of determining the dose-response function for different routes of administration in evaluating the biochemical and behavioral effects of psychostimulants.

The purpose of the present study was to assess the effects of oral MP (intragastric administration) on extracellular DA in NACC and on locomotor activity. In addition, we directly compared the effects of oral versus i.p. MP to provide a context for evaluation of the findings from previous studies. The range of doses used (2–10 mg/kg) is, in general, lower than those investigated previously. Finally, we compared two methods of oral MP administration, a surgically implanted intragastric catheter versus gavage, to determine whether the stress associated with gavage would influence the effects of MP on NACC DA.

Materials and Methods

Male Sprague-Dawley rats were used in all experiments (200–300 g; Taconic Farms, Germantown, NY) and were given food and water ad libitum. Temperature and humidity were kept constant. Each animal was housed individually on a 12/12-h light/dark cycle. All animals were used under an Institutional Animal Care and Use Committee-approved protocol and with strict adherence to National Institutes of Health guidelines.

Drug Treatment. MP hydrochloride (2, 5, or 10 mg/kg) (a racemic mixture of *d-threo-* and *l-threo*-MP; Research Biochemicals International, Natick, MA) was dissolved in saline and injected i.p. Intragastric administration (2, 5, or 10 mg/kg) was accomplished through the preimplanted catheter followed by a rinse with vehicle. Control animals received saline via both routes. These same methods were used with microdialysis and locomotor activity studies. In a separate microdialysis experiment MP (5 mg/kg) or vehicle was administered via a gavage needle that was gently passed down the esophagus to the stomach (n = 6–8 for each treatment group). All microdialysis and activity measures were obtained between 12:00 PM and 3:00 PM.

Microdialysis Studies. Microdialysis studies were completed as detailed previously (Gerasimov and Dewey, 1999). Animals were anesthetized with an i.m. injection of ketamine/xylazine mixture and siliconized guide cannulas were stereotaxically implanted into the

right NACC (2.0 mm anterior and 1.0 mm lateral to bregma, and 7.0 mm ventral to the cortical surface). On completion of the brain surgery a polyethylene catheter was placed in the stomach of animals intended for intragastric studies by using aseptic surgical techniques. The catheter was exteriorized after anchoring with a suture in the back of the neck. Animals were allowed to recover for at least 4 days.

Microdialysis probes (2.0 mm; Bioanalytical Systems, West Lafayette, IN) were positioned within the guide cannulas and artificial cerebrospinal fluid (155 mM NaCl, 1.1 mM CaCl$_2$, 2.9 mM KCl, and 0.83 mM MgCl$_2$) was administered through the probe by using a CMA/100 microinfusion pump (Bioanalytical Systems) at a flow rate of 2.0 l/min. Animals were placed in bowls, and probes were inserted and flushed with artificial cerebrospinal fluid overnight. On the day of study, a minimum of three samples was injected to determine baseline stability. Samples were collected for 20 min and injected on-line (Bioanalytical Systems). The average DA concentration of these three stable samples was defined as control (100%), and all subsequent treatment values were transformed to a percentage of that control. The HPLC system consisted of a BAS reversed phase column (3.0 μm C18), a BAS LC-4C electrochemical transducer with a dual glassy carbon electrode set at 650 mV relative to an Ag/AgCl reference electrode, a computer that analyzes data on-line by using a commercial software package (Chromgraph; Bioanalytical Systems), and a dual pen chart recorder. The mobile phase (flow rate 1.0 ml/min) consisted of 7.0% methanol, 50 mM sodium phosphate monobasic, 1.0 mM sodium octyl sulfate, and 0.1 mM EDTA, pH 4.0.

Locomotor Activity. Animals were individually placed in photocell activity boxes (San Diego Instruments, San Diego, CA). The boxes were 41.3 × 41.3 × 30.5-cm clear acrylic. The electronic system used to monitor the movements consists of 16 infrared beams projecting across the cages from left to right and 16 beams from back to back. All the beams are approximately 0.39 cm from the floor. After 100 min to allow initial exploratory behavior to decrease, animals were injected i.p. with vehicle or MP (2, 5, or 10 mg/kg). In a separate group of experiments, animals received saline or MP (2, 5, or 10 mg/kg) by intragastric infusion via a catheter. Beam crossings were recorded every minute and the mean number of crossings for each group of animals was summed into 20-min intervals for graphical display.

d-[^{3}H]$threo$-MP Uptake in the Brain. Animals were treated with 5 mg/kg MP plus 2 μCi (per rat) of d-[^{3}H]$threo$-MP either i.p. or via gavage. After 20 min animals were sacrificed by decapitation and their striata and cerebella dissected. Brain regions were weighed and dissolved in 1 ml of tissue solubilizer (Solvable; Packard, Meriden, CT). UltimaGold (Packard) liquid scintillation fluid was added and radioactivity was determined by scintillation counting with quench connection by external standard. Data are expressed as nanomoles of d-[^{3}H]$threo$-MP per gram of tissue (wet weight).

Data Analysis. Peak increases in extracellular DA, expressed as a percentage of baseline values (the average of three predrug levels differing from each other by not more than 10%) were compared for every dose across both routes of administration by a one-way ANOVA and post hoc test. Significance levels were set at $P < .05$.

For comparison purposes, the increases in NACC DA levels were normalized to the highest value for each dose and expressed as a percentage of that value. Locomotor activity reflects the highest beam crossing count after subtraction of the baseline activity.

Results

Microdialysis Studies. Intraperitoneal injections of MP dose dependently increased extracellular NACC DA above vehicle treatment values (F = 26.75; $P < .05$, $P < .01$, $P < .001$ for 2, 5, and 10 mg/kg, respectively). Intragastric administration also produced an increase in DA levels ($P < .05$ and $P < .001$ for 5 and 10 mg/kg, respectively). However, the

measured response after intragastric administration of 2 mg/kg did not reach statistical significance. For both routes of administration and all three doses, the maximal effect of MP occurred at 40 min with levels returning to baseline values approximately 2.5 h postadministration (Fig. 1). During the first 20 min after administration the values approximately doubled for i.p. injection, but increased only by 30% after intragastric administration (Fig. 1, B and C), consistent with a faster rate of DA increase after the i.p. route.

Administration of 5 mg/kg MP by gavage produced in-

creases in DA levels that did not significantly differ from those produced by intragastric administration. The temporal profile of increases in extracellular DA after gavage administration is identical with the time course of increases after administration of the same dose via intragastric catheter (Fig. 2).

Locomotor Activity. Similar to our microdialysis data, i.p. injections of MP dose dependently increased gross locomotor activity above vehicle treatment values (Fig. 3) ($F = 36.68$; $P < .05$, $P < .01$, $P < .001$ for 2, 5, and 10 mg/kg, respectively. Intragastric administration, however, resulted in increased locomotion only after 5- and 10-mg/kg doses ($P < .01$, $P < .001$). On average, the maximal response for i.p. administration occurred at 20 min, whereas for intragastric administration it occurred at 40 min postdrug administration. For each dose examined, the DAergic and locomotor response to i.p. MP was significantly greater than the response after intragastric administration (Figs. 4 and 5).

The relationship between the temporal course of the changes in extracellular DA and locomotor activity is represented as a normalized response (Fig. 6). Because there was no change in either extracellular DA or locomotion after intragastric administration of 2 mg/kg, Fig. 5A shows only the response to i.p. injection.

Brain and Plasma Levels of MP. Intraperitoneal administration of [^{3}H]MP resulted in higher levels of radioactivity in plasma and brain than the intragastric route (Table 1).

Discussion

This study shows that intragastric and i.p. routes of administration differ significantly with respect to the absolute magnitude and the time course of increases in extracellular DA and locomotor response. Intraperitoneal MP was approximately twice as potent as oral MP both in increasing extracellular DA levels at the doses of 5 and 10 mg/kg (Fig. 1A) and in stimulating locomotor activity at these same doses (Fig. 1B). This is consistent with the apparent higher uptake of [^{3}H]MP measured in the brain after i.p. versus intragastric administration (Table 1). However, the interpretation of the brain uptake results is limited by the inaccuracy of assessing
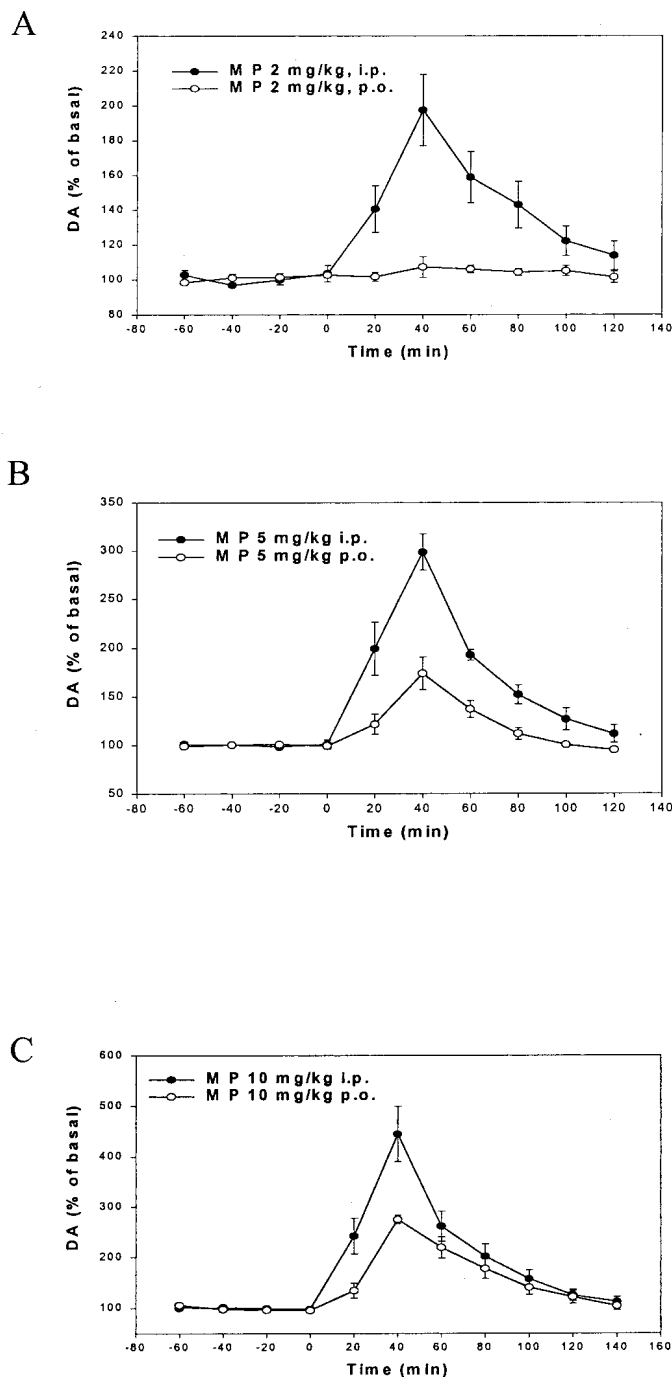

Fig. 1. Temporal profile of i.p. or intragastrical (p.o.) MP effect on extracellular NACC DA. A, effects of 2 mg/kg MP. B, effects of 5 mg/kg MP. C, effects of 10 mg/kg MP. Values are expressed as percentage of baseline DA and are mean ± S.E. ($n = 6-8$/group). Drug or vehicle was administered at time 0. For clarity saline response is not shown.
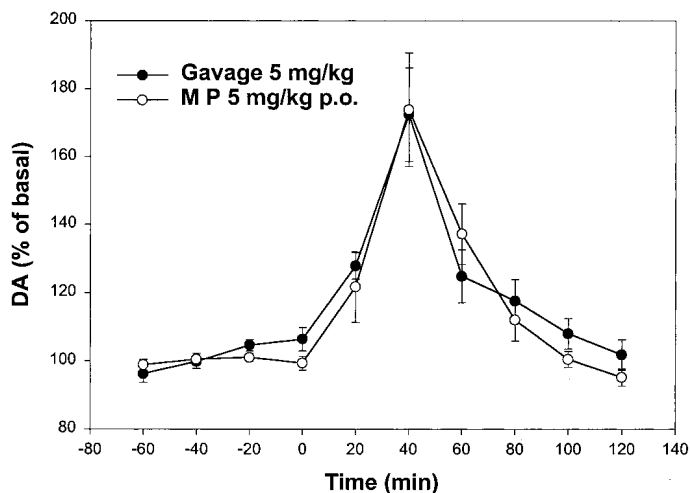

Fig. 2. Temporal profile of 5 mg/kg intragastrical (p.o.) and gavage MP effect on extracellular NACC DA. Values are expressed as percentage of baseline DA and are mean ± S.E. ($n = 6-8$/group). Drug was administered at time 0.
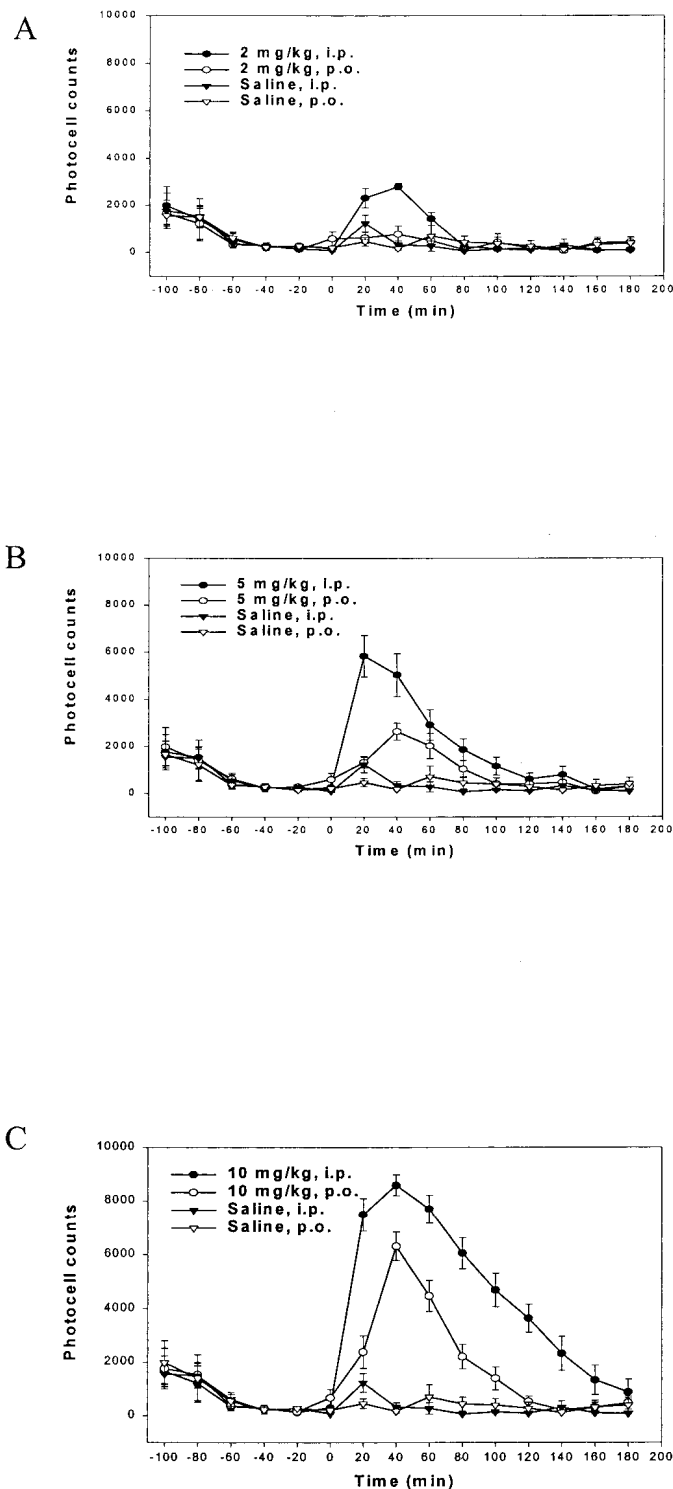
A

B

C

Fig. 3. Temporal profile of i.p. or intragastrical (p.o.) MP effect on gross locomotor activity. A, effects of 2 mg/kg MP. B, effects of 5 mg/kg MP. C, effects of 10 mg/kg MP. Values are expressed as the number of beam crossings and are mean ± S.E. (n = 6–8/group). Drug or vehicle was administered at time 0. For clarity saline response is not shown.

the total radioactivity counts without isolating [^{3}H]MP from ^{3}H-metabolites. Interestingly, at the lowest dose of 2 mg/kg given intragastrically, we did not observe an increase in DA levels above vehicle treatment nor was there any change in locomotor activity. In contrast, that same dose administered
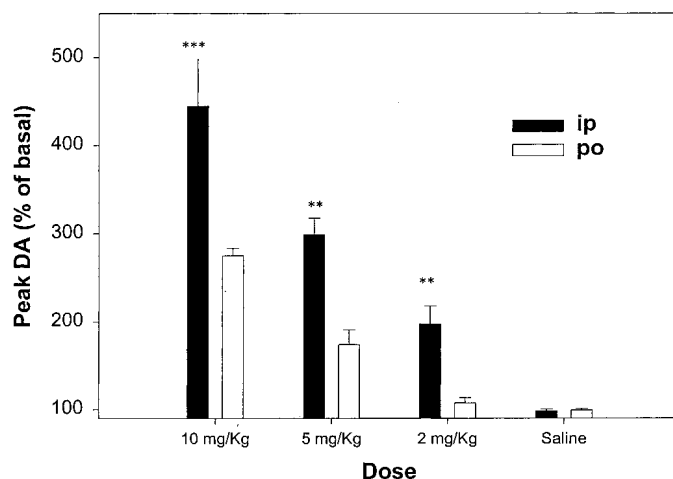

Fig. 4. Peak increase in NACC DA in response to i.p. or intragastrical (p.o.) administration of MP. Values are expressed as percentage of baseline DA and are mean ± S.E. (n = 6–8/group). ***$P < .001$, **$P < .01$ compared with the effect of the identical dose administered via different route [ANOVA (F = 26.75) and post hoc Tamhane test].
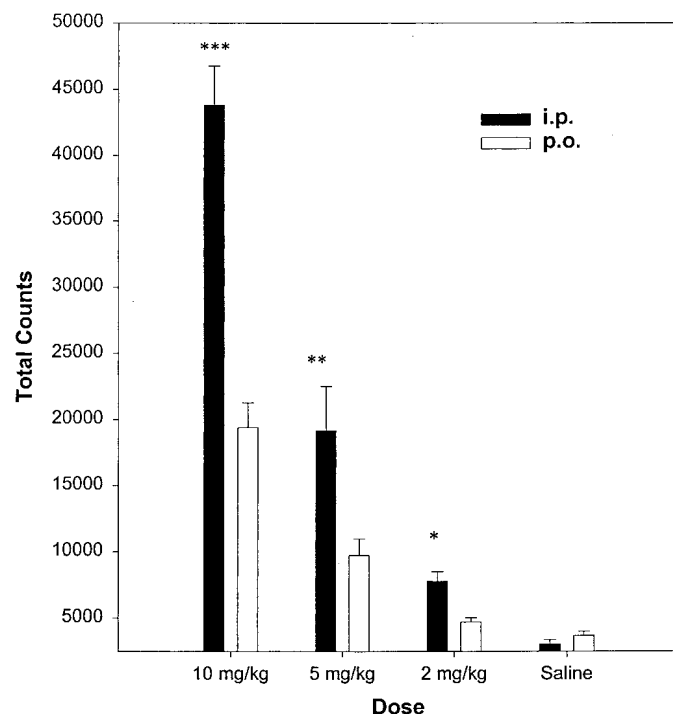

Fig. 5. Locomotor response to i.p. or intragastrical (p.o.) administration of MP. Values are expressed as total number of beam crossings over 200-min time interval and are mean ± S.E. (n = 6–8/group). ***$P < .001$, **$P < .01$, *$P < .05$ compared with the identical dose administered via different route [ANOVA (F = 36.68) and post hoc Tamhane test].

i.p. produced a significant increase above baseline values in extracellular DA and in locomotion. These data are in agreement with the notion that quantitatively different responses to identical doses of MP administered to humans via two systemic routes (i.v. and oral) are a function of bioavailability (Chan et al., 1980). The lower bioavailability for intragastric versus i.p. MP is presumably due to the slower absorption from the gastrointestinal tract and a greater degree of metabolism to ritalinic acid, a compound with negligible psychostimulant properties (Faraj et al., 1974).

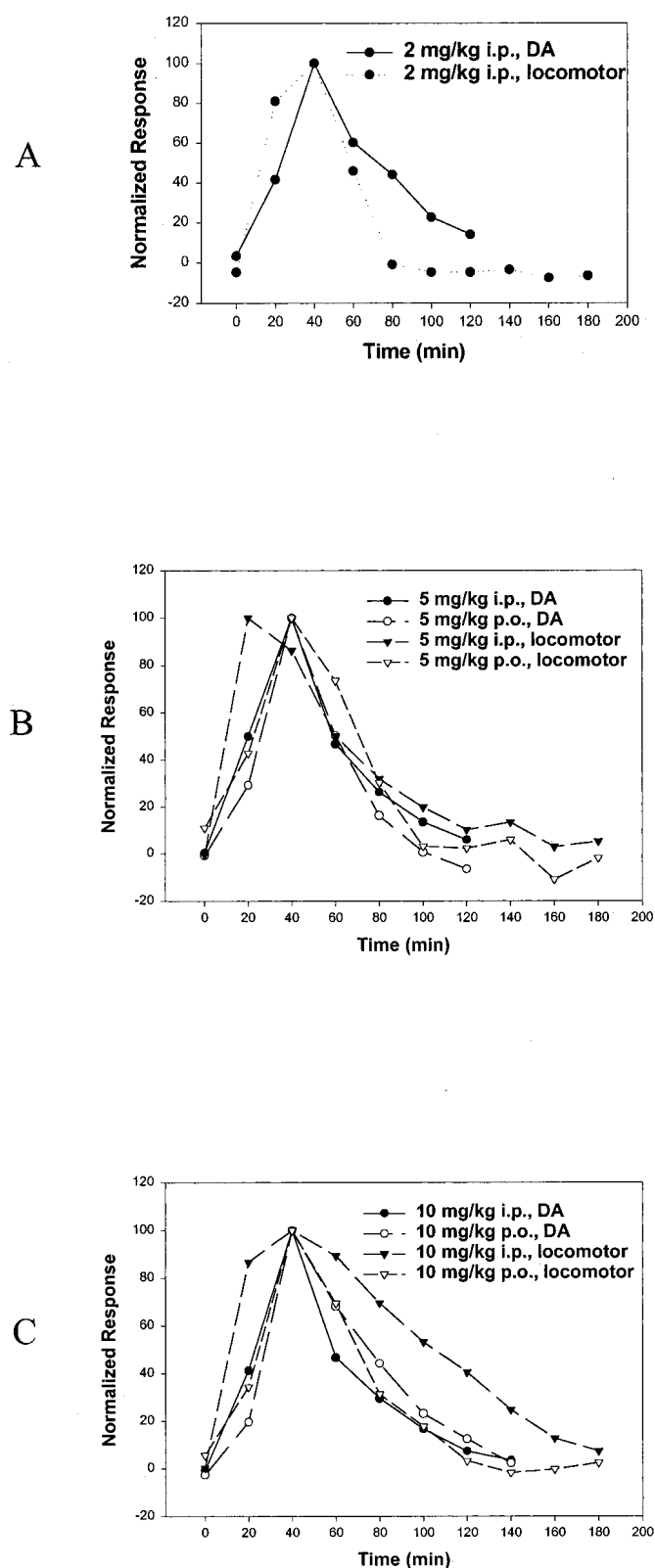Overall, quantitative and qualitative differences between

A

B

C

Fig. 6. Normalized NACC DA and locomotor temporal response to MP. Values are expressed as the percentage of the maximum for each given function and represent the average of six animals. Drug was administered at time 0.

oral, i.p., and i.v. routes of administration have been demonstrated for MP across species (Faraj et al., 1974; Wargin et al., 1983). However, the reports are varied and sometimes

TABLE 1

d-[^{3}H]$threo$-MP or metabolite(s) concentrations (nmol/g) in brain and plasma after administration of 5 mg/kg MP via gavage or intraperitoneal injection

Values are mean ± S.D. Superscript letters correspond to post hoc t tests showing significant difference of intraperitoneal injection from gavage (oral).

Route	Cerebellum	Striatum	Plasma
Oral	5.2 ± 1.8	6.4 ± 3.2	4.2 ± 0.91
Intraperitoneal	13 ± 6.7[a]	16 ± 9.1[a]	11.2 ± 6.2[b]

[a] $P < .05$.
[b] $P < .001$.

inconsistent. This may reflect considerable intersubject variability due to differences in drug absorption and metabolism. Studies by Faraj et al. (1974), Wargin et al. (1983), and Chan et al. (1980) provide evidence for presystemic metabolism of MP via deesterification in the gut and microsomal hydroxylation in liver as well as high intrinsic clearance due to plasma and/or tissue esterase activity. Reported estimates of the absolute systemic bioavailability of oral MP in children, rats, and monkeys vary between 10 and 50%.

Gross locomotor activity observed at 10 mg/kg i.p. does not seem to increase further with a higher dose of 20 mg/kg (O. Rice and S. J. Gatley, unpublished observations) even though extracellular NACC DA levels are increased further (860 versus 480% of baseline) (Rice et al., 1998). This is presumably due to focused stereotypies interfering with horizontal movements of the animal (Gaytan et al., 1996).

For both routes of administration gross locomotor activity responses to MP approximately track increases in NACC DA. This is consistent with the hypothesis that facilitation of DAergic transmission is involved in the locomotor response to psychostimulants (Beninger, 1983). The intragastric route exhibited a very close parallelism for the behavioral and neurochemical responses to MP, even though these measurements were obtained in different groups of animals. Normalized plots of extracellular DA and locomotor activity are almost identical (Fig. 6, A and B). However, for i.p. administration the quantitative features of MP-induced behavioral activation were dissociated from increases in extracellular DA. Peak hyperactivity occurred at 20 min postadministration, whereas the DA response took 40 min to reach its maximum. Between 20 and 40 min locomotor activity was almost constant, whereas extracellular DA continued to increase. Although this could reflect a ceiling effect for locomotor activity, after which further DA increases result in stereotypies, it also could reflect acute tolerance to the locomotor-activating effects of synaptic DA, occurring after the fast initial increase in DA concentrations. A similar dissociation between plasma levels and therapeutic efficacy has been reported for oral MP in children (Swanson et al., 1999). The time course of plasma and brain MP concentration changes appears to be crucial in determining the efficacy of this drug (Srinivas et al., 1992). This notion was recently emphasized by Swanson et al. (1999) who demonstrated that the efficacy of a given total dose of MP is affected by its rate of administration.

A dissociation between DA and locomotor activity for the i.p. route of administration also was observed for the declining portion of the curves for the 10-mg/kg dose because at 120 min postinjection DA levels were already returning to baseline, whereas locomotion remained significantly elevated. This also could have reflected a ceiling effect and we cannot

rule out the possibility that as DA levels fell stereotypy decreased concomitantly. New studies are now being designed with the goal of assessing the temporal course of stereotypies. Alternatively, this dissociation could reflect lingering downstream effects.

Another explanation is based on the partial involvement of the noradrenergic neurotransmitter system in the locomotor response to stimulants (Svensson and Ahlenius, 1983). We previously demonstrated that MP binds to norepinephrine transporters and is an effective in vitro inhibitor of norepinephrine uptake (Gatley et al., 1996). Kuczenski and Segal (1997) demonstrated that the temporal profile of the hippocampal norepinephrine response to i.p. MP in rats is significantly different from that of DA, with a slower onset and longer duration.

For the highest MP dose tested (10 mg/kg) the difference in locomotor activity between the two routes is better demonstrated by comparing the areas under the curve (total movements count over the sampling period) rather than the peak effects (Figs. 3 and 5) because the magnitudes of peak activity were similar, but i.p. MP had a much longer-lasting effect. This is likely to reflect almost complete DA transporter saturation at this dose for both routes, but the higher bioavailability achieved with the i.p. route may result in a longer duration of DA transporter blockade at this high level of occupancy.

In extrapolating the results of this study to the effects of clinical doses of MP the question of a proper dose for comparison arises. Matching of the peak MP plasma concentrations in humans and in rats does not seem to be appropriate for choosing a clinically relevant dose to be administered to animals. Concentrations that are considered therapeutic (8–10 ng/ml) (Swanson and Volkow, 2000) are reached at an average of 1 to 1.5 h after administration and roughly coincide with the peak changes in behavioral and somatic variables. The average half-life of oral MP is reported to be 2 to 3 h (Wargin et al., 1983; Volkow et al., 1998). However, similar plasma levels in the rat are only achieved for a short period of time (1.4–25 ng/ml at 15 min) and are almost undetectable at 30 min (0–4 mg/ml) (T. Cooper, personal communication). According to Patrick et al. (1984), oral administration of 1 mg/kg MP in rats results in peak serum concentrations of 40 ng/ml that are reached 10 min after dosing, but which fall to 15 ng/ml during the next 5 min. However, when 10 mg/kg oral MP is administered to rats, the half-life of MP appears to be 1 h with the plasma levels of 40 ng/ml occurring 3 h after drug administration (Wargin et al., 1983) or 10 to 20 ng/ml 4 h after 20 mg/kg (T. Cooper, personal communication). Based on these data one might argue that the lowest dose of oral MP (2 mg) used in the present study is not of clinical relevance due to its short-lived effective concentrations in plasma and subsequently, brain concentrations. However, the intragastric dose of 10 mg/kg leads to sustained plasma levels that are higher than those achieved therapeutically. The intermediate MP dose of 5 mg/kg administered intragastrically might mimic the therapeutic doses better. In terms of the magnitude of neurochemical and behavioral effects, the 5-mg/kg intragastric dose was roughly equivalent to the 2-mg/kg i.p. dose. Thus, by extrapolation one could suggest that i.p. MP doses of less than 5 mg/kg may be closer to those used clinically. However, one should keep in mind that therapeutic effect of MP in humans

requires sustained brain levels, which are not achieved in rats.

In this study we did not observe a difference between the DAergic responses to MP administered intragastrically or via gavage. This indicates that both methods are adequate for testing the effects of oral MP.

Investigation of the relative effects of oral and i.p. MP is of basic and clinical significance. Low reinforcing effects of oral versus i.v. MP in humans have been linked to differences in pharmacokinetics rather than poor binding efficacy at the DA transporter (Volkow et al., 1998). Additionally, several studies have shown that the effects of MP are dependent on the behavioral state of the subject. This effect described as "rate dependence" has been documented both in rats and in humans (Rapport et al., 1984; Weber, 1985). Our results demonstrate that the route of administration is an important determinant of the behavioral and neurochemical consequences associated with MP administration in rodents. Additionally, we are currently conducting new studies investigating the changes in brain DA elicited by therapeutic doses of MP in humans.

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